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09/756,214	01/09/2001	Kenji Yamashita	Q62578	4067

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/756,214	YAMASHITA ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27 and 29-33* is/are pending in the application.

4a) Of the above claim(s) *31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *27,29,30 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/254,170.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 27, 29-32, and newly added Claim 33, are pending.

2. Claims 31 and 32 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species of the elected invention.

3. Applicant's remarks filed 11/08/04 are acknowledged.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 27, 29, 30, and newly added Claim 33, stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U. S. Patent No. 6,171,799 in view of Schwarz et al. (1995), Chavin et al. (1994), Chavin et al. (1993), and Jones et al. (1992), for the reasons of record.

As set forth previously, the '799 patent teaches a culture device for the culturing of immunosuppressive (suppressor) cells, with an affinity for protein, wherein prior to cell culturing the culture device is coated with an anti-CD3 antibody (OKT3) (see particularly column 33, lines 30-53).

The reference differs from the claimed invention in that it does not teach a device further coated with an $F(ab)_2$ fragment of the anti-CD2 antibody TS2/18 antibody produced by the hybridoma HB195.

Schwarz et al. teaches the culture of T cells with the anti-CD2 TS2/18 antibody and that said culture results in inhibitory effects on T cell activation (see particularly page 5816, column 1, paragraph 4). The reference further teaches that the epitope recognized by TS2/18 is a candidate for CD2-directed immunosuppression (see particularly page 5817, column 2, paragraph 3).

Chavin et al. (1994) teaches that anti-CD2 antibodies can be used to generate Th2 suppressor cells (see particularly Results, *Anti-CD2 mAb induces suppressor cells*) and that various anti-CD2 antibodies are interchangeable (see particularly the sentence spanning pages 3729 and 3730).

Chavin et al. (1993) teaches that anti-CD2 and anti-CD3 antibodies synergize in an immunosuppression context (see particularly Discussion, column 1, second paragraph).

Jones et al. teaches the interchangeability of whole antibodies and $F(ab)_2$ fragments for the coating of devices (plastic plates) for the incubation of lymphocytes (see particularly page 236, column 1, second paragraph). The reference further teaches that in some situations an $F(ab)_2$ fragment is preferable, such as when the reduction of a background signal is desirable, (see Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a culture device for the culturing of immunosuppressive (suppressor) cells, wherein prior to cell culturing the culture device is coated with an anti-CD3 antibody, as taught by the '799 patent, additionally coating the plate with a an anti-CD2 TS2/18 antibody, as taught by the Schwarz et al., employing either the whole antibody or an $F(ab)_2$ fragment of said antibody, given the fact that whole antibodies and $F(ab)_2$ fragments are interchangeable and in some situations an $F(ab)_2$ fragment is preferable, as taught by Jones et al. One of ordinary skill in the art would have been motivated to double-coat (anti-CD2 and anti-CD3) the plate given the teachings of Chavin et al. (1994) that anti-CD2 antibodies can be used to generate Th2 suppressor cells and that various anti-CD2 antibodies are interchangeable and Chavin et al. (1993) that anti-CD2 and anti-CD3 antibodies can synergize in an immunosuppression context. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06). Thus, the combination of antibodies would be obvious.

Applicant's arguments, filed 11/08/04, have been fully considered but they are not persuasive. Applicant argues, "none of the references teaches a device for culturing immunosuppressive cells with an ability to suppress hypersensitivity of an immune system which causes autoimmune disease".

This limitation would seem to be a property of the device itself. Thus, no matter how, or for whatever reason, the device was produced, the device would encompass the claimed property. Also note that Applicant has broadened Claims 27, 29, and 30 to include a device employing *any* anti-CD2 $F(ab)_2$, thus, indicating agreement with the prior art that the fragments are interchangeable.

Applicant asserts, "the immunosuppressive cells induced by the present invention suppress particular T cells, i.e. T cells activated with PPD, which is regarded as a causative agent of autoimmune diseases".

Note that none of the claims recite suppressing PPD activated T cells, regardless, the specification provides no evidence that the asserted suppression is antigen specific

because the proper controls were not included in the experiments. Regarding the assertion that PPD causes autoimmune diseases, see Section 11 below.

Applicant argues that the device of the EP'380 document targets the induction of cytotoxic cells and clearly differs from the instant device.

See Section 9 below.

Applicant argues that Schwarz et al. would discourage the use of TS2/18 "to activate T cells and to thereby induce immunosuppressive cells".

Applicant is advised that the motivation of the combined references need not be the same as that of the Inventors. In the instant case, the combination of anti-CD2 and anti-CD3 antibodies was known to be immunosuppressive, and TS2/18 was a well-known anti-CD2 antibody. Regardless of the actual mechanism of immunosuppression induction, the combination of known immunosuppressive antibodies would have been obvious to the ordinarily skilled artisan at the time of the invention.

Applicant argues that Chavin et al. (1994) teaches the induction of suppressor cells employing anti-CD2 antibodies *in vivo* whereas the device of the instant claims is used *in vitro* and that anti-CD2 $F(ab)_2$ was not as effective as whole anti-CD2.

Applicant's observation that *in vivo* and *in vitro* processes are quite different is not in itself a persuasive argument as to why the skilled artisan would not expect an antibody that induced suppressor cells *in vivo* to also be capable of producing suppressor cells *in vitro*. And note that while the reference may indicate that in one context whole anti-CD2 was more effective than anti-CD2 $F(ab)_2$, anti-CD2 $F(ab)_2$ was still effective.

Regarding the Jones et al. reference, the reference is merely used to teach that in the context of coating plates, whole antibodies and $F(ab)_2$ fragments are often interchangeable an in some contexts $F(ab)_2$ fragments are preferred.

Regarding Applicant's assertions of synergy in employing anti-CD2 $F(ab)_2$ and anti-CD3 antibodies together, as opposed to employing them separately, Applicant asserts that, "According to TEST EXAMPLE 1 of the present specification, the effect of the present invention is that activity of T cells is suppressed 78%,

in contrast to when F(ab)2 fragment of anti-CD2 antibody alone and anti-CD3 antibody alone are used, whereby the activity is suppressed 20% and 50% respectively. Hereinafter, it is described that the result of 78% suppression is an unexpected and synergistically increased effect."

A review of the specification shows that Applicant has slightly, but significantly, misrepresented the disclosed results. The specification discloses "about" 78% suppression combined, as compared to "about" 20% and "about" 50% suppression individually. Additionally, a review of Figure 6 in which the actual results are disclosed reveals an error approaching 50% of the measured suppression with anti-CD2 $F(ab)_2$ and anti-CD3 antibody. Thus, Applicant's assertion regarding synergy is not found convincing given the fact that "about" 20 and "about" 50 can be considered to be "about" 78.

Applicant cites unrelated literature and concludes with an assertion that the combined effect of anti-CD2 $F(ab)_2$ and anti-CD3 antibody would be at most 50% suppression.

Applicant is advised that an attorney's assertion as to what one of skill in the art would expect is not found to be convincing.

6. Newly added Claim 33 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over EP 0421380A1 (1990) in view of Schwarz et al. (1995), Chavin et al. (1994), Chavin et al. (1993), and Jones et al. (1992), for the reasons of record.

As set forth previously, EP 0421380A1 teaches a culture device (see particularly page 4, line 16) coated with an anti-CD3 antibody and an anti-CD2 antibody (see particularly page 3, lines 26-27) including an enzymatically cleaved antibody fragments (see particularly page 3, lines 33-36).

The reference differs from the claimed invention in that it does not teach the specific anti-CD2 antibody TS2/18 produced by the hybridoma HB195 nor the use of an $F(ab)_2$ fragment.

Schwarz et al. teaches the well known anti-CD2 antibody TS2/18 produced by the hybridoma HB195 (see particularly Abstract)).

Chavin et al. (1994) teaches that anti-CD2 antibodies can be used to generate Th2 suppressor cells (see particularly Results, *Anti-CD2 mAb induces suppressor cells*) and that various anti-CD2 antibodies are interchangeable (see particularly the sentence spanning pages 3729 and 3730).

Chavin et al. (1993) teaches that anti-CD2 and anti-CD3 antibodies synergize in an immunosuppression context (see particularly Discussion, column 1, second paragraph).

Jones et al. teaches the interchangeability of whole antibodies and $F(ab)_2$ fragments for the coating of devices (plastic plates) for the incubation of lymphocytes (see particularly page 236, column 1, second paragraph). The reference further teaches that in some situations an $F(ab)_2$ fragment is preferable, such as when the reduction of a background signal is desirable, (see Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a culture device coated with an anti-CD3 antibody and an anti-CD2 antibody, given the teachings of Chavin et al. (1994) that anti-CD2 antibodies can be used to generate Th2 suppressor cells and that various anti-CD2 antibodies are interchangeable and Chavin et al. (1993) that anti-CD2 and anti-CD3 antibodies synergize in an immunosuppression context, including an enzymatically cleaved fragments of an anti-CD2 antibody as taught by EP 0421380A1, employing the TS2/18 anti-CD2 antibody produced by the hybridoma HB195, as taught by Schwarz et al, because the TS2/18 anti-CD2 antibody was well known and readily available, employing either the whole antibody or an $F(ab)_2$ fragment of said antibody, given the fact that whole antibodies and $F(ab)_2$ fragments are interchangeable and in some situations an $F(ab)_2$ fragment is preferable, as taught by Jones et al.

Applicant has not argued this rejection separately. See Section 5 above.

7. The following are new grounds for rejection necessitated by Applicant's amendment.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States

9. Claims 27, 29, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0421380A1 (1990).

EP 0421380A1 teaches a culture device (see particularly page 4, line 16) coated with an anti-CD3 antibody and an anti-CD2 antibody (see particularly page 3, lines 26-27) including an enzymatically cleaved antibody fragments (see particularly page 3, lines 33-36). Note, under *In re Schauman*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978), claims to a specific compound were anticipated because the prior art taught a generic formula embracing a limited number of compounds closely related to each

other in structure and the properties possessed by the compound class of the prior art was that disclosed for the claimed compound. In the instant context, given the extremely limited number of functional enzymatically cleaved antibody fragments that could be envisioned, e.g., F(ab) or $F(ab)_2$, all would be anticipated.

The reference clearly anticipates the claimed invention.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 27, 29, 30, and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *in re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Regarding novel methods involving biological processes, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature

of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)". The MPEP further states that physiological activity can be considered inherently unpredictable.

Given the established unpredictability of the art, the instant specification must disclose sufficient evidence that the device of the instant claims is capable of inducing cells "wherein said immunosuppressive cells have an ability to suppress hypersensitivity of an immune system which causes autoimmune disease".

A review of the specification discloses that the only autoimmune disease disclosed is MS (and then only briefly in the Background section) and the only antigen disclosed is PPD (the antigen of the Examples). It is noted, however, that no connection is even asserted between PPD and MS, and certainly none has been established. In the arguments of 11/08/04, Applicant asserts, "PPD, which is regarded as a causative agent of autoimmune diseases (see Test Example 1)"; yet nowhere in the Example is PPD established to be, nor even referred to, as "a causative agent of autoimmune diseases". Indeed, a review of the relevant art shows that, contrary to Applicant's assertion, PPD appears to be *protective* of autoimmune disease. See for example, Ben-Nun et al (1995), wherein it is taught that PPD protects mice against EAE (Abstract). The reference goes on to suggest that PPD might be used in autoimmune disease therapy (Discussion). See also, Bromelow et al. (1997) wherein the authors teach that suppression of a PPD response correlated with autoimmune disease (IDCM) progression (Abstract). While the latter reference does not conclude that a PPD response would be immunoprotective, it certainly casts additional doubt on Applicant's unsupported assertion that PPD causes autoimmune disease. Absent a connection between PPD and autoimmune disease, the newly added limitation that the claimed device is capable of inducing "immunosuppressive cells have an ability to suppress hypersensitivity of an immune system which causes autoimmune disease" finds no support in the instant specification and is actually contradicted by the prior art. Accordingly, the invention is considered to be highly unpredictable and requiring of undue experimentation to practice as claimed.

12. No claim is allowed.

13. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Inquiries of a general nature may also be directed to the Technology Center 1600 Receptionist at (571) 272-1600.

2/4/05

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